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(54) Title: PHARMACEUTICAL AND/OR COSMETICAL COMPOSITIONS

(57) Abstract: The present invention relates to pharmaceutical and/or cosmetical compositions comprising from 0.5 to 1.5 wt % of one or more compounds selected from the group consisting of Titrated Extract of Centella Asiatica (TECA), asiaticoside, asiatic acid and madecassic acid, and from 4 to 6 wt % of pantothenic acid and/or its derivatives. The compositions according to the present invention show an important activity in the neosynthesis of collagens, in contrast to compositions containing separately the same amount of the two active compounds. They are suitable for treating dermatological disorders such as wound-healing, chronic venous insufficiency, skin aging, wrinkling, laxity, cellulite and photodamage.

Pharmaceutical and/or cosmetical compositions

The present invention relates to pharmaceutical and/or cosmetical compositions for treating dermatological disorders such as wound-healing, chronic venous insufficiency, skin aging, wrinkling, laxity, cellulite and photodamage.

5 It is known that compositions containing pantothenic acid and/or its derivatives are useful for healing wounds and for treating further dermatological disorders.

Pantothenic acid, which is also known as D(+) N-(2,4-dihydroxy-3,3-dimethylbutyryl) $\beta$ -alanine, is a member of the B complex vitamins and is sometimes referred to as vitamin B5.

10 Pantothentic acid plays a key role in cellular metabolism, as after incorporation into coenzyme A (CoA), it participates in the synthesis of fatty acids, cholesterol and sterols. Through its participation in the Krebs cycle, coenzyme CoA is also instrumental in the generation of energy by the cells. Pantothentic acid is hence essential for epithelial regeneration and development in the event of damage to the skin when a high rate of lipids and cellular renewal is needed.

15 Dexpanthenol, the alcohol of the pantothenic acid, is well absorbed by the skin. After penetration in the skin it is rapidly transformed into pantothenic acid. Dexpanthenol has therefore been used for many years in topical products such as ointments and creams. The clinical effectiveness of the topical application of dexpanthenol in promoting wound healing has been confirmed by several studies in cases of wounds, burns, cracked nipples, 20 ulcers, and bedsores (e.g. P.Girard, A.Béraud, C.Goujon, A.Sirvent, J-L Foyatier, B. Alleaume, R. de Bony, *Les Nouvelles Dermatologiques*, 17, 1998, pp 559-570).

25 Centella Asiatica is a plant of the umbelliferae family and has been used for wound healing. Centella Asiatica is also suitable for cosmetic use such as skin conditioning improvement and anti-cellulite effect. Centella Asiatica contains asiatic acid, madecassic acid and asiaticoside, all of which belong to the class of triterpenoids. Titrated Extract of Centella Asiatica (TECA, Serdex) is a combination of 40 wt % asiaticoside and 60 wt % of the two genines asiatic acid and madecassic acid.

- 2 -

Titrated Extract of *Centella Asiatica* is commercially available under the trademark **MADECASSOL®** or can be prepared by maceration of dried plants of *Centella Asiatica* and various purification steps. (*International Cosmetic, Ingredient Dictionary*, 5th Edition, 1993, Editors: John A. Wenninger et al, published by The Cosmetic, Toiletry, and Fragrance Association).

Asiatic acid, asiaticoside and madecassic acid are known and commercially available compounds and can be prepared as described in "International Cosmetic, Ingredient Dictionary", 5th Edition 1993, Editors: John A. Wenninger et al, published by The Cosmetic, Toiletry, and Fragrance Association.

10 It has been now surprisingly found that compositions comprising from 0.5 to 1.5 wt % of one or more compounds selected from the group consisting of Titrated Extract of *Centella Asiatica* (TECA), asiaticoside, asiatic acid and madecassic acid, and from 4 to 6 wt % of pantothenic acid and/or its derivatives, show an important activity in the neosynthesis of collagens, in contrast to compositions containing separately the same amount of the two 15 active compounds.

The synergistic action of the two compounds tested in association enables therefore to provide therapeutically active pharmaceutical and/or cosmetical compositions with enhanced potency. Compositions with higher therapeutic activity are therefore obtained without enhancing the amount of active compounds and, therefore, without 20 compromising the patient's tolerance of the active principles and without increasing the manufacturing costs.

The compositions according to the present invention can contain asiatic acid, asiaticoside and madecassic acid, singly or in any combination thereof. Preferably, the composition according to the present invention comprises 0.5 to 1.5 wt % of TECA.

25 Any pharmaceutically and/or cosmetically acceptable derivative of pantothenic acid can be used in the compositions of the present invention. Examples include alcohols, aldehydes, alcohol esters, acid esters and the like. The preferred derivative of pantothenic acid is pantothenyl alcohol (panthenol), particularly the D(+) of pantothenyl alcohol which is more commonly known as dexpanthenol. As preferred alcohol ester, pantothenyl triacetate 30 can be chosen.

The composition according to the present invention may further comprise additional vitamins such as vitamin A, vitamins B other than pantothenic acid, vitamin C and vitamin E. Vitamins B other than pantothenic acid, vitamin C and/or vitamin E can be present in an amount varying from 0.01 wt % to 10.0 wt %, while Vitamin A can be suitably used in 35 concentrations from 1000 to 5000 IU per gram of composition.

If used for treating chronic venous insufficiency, the composition according to the present invention may contain active principles for this purpose. Examples thereof are escin, rutosides and mixtures thereof. They can be incorporated into the composition either in pure form or by means of natural extracts containing them. A preferred extract containing 5 escin is that of Horse Chestnut, while preferred extracts containing rutosides are those of Sophora Japonica and Gingko Biloba.

According to the present invention, the composition may also contain minerals for supporting the regeneration and maintenance of human tissues such as the skin and/or the 10 blood vessel tissues. Such minerals are preferably selected from those including Se, Zn, Mg and Ca.

The pharmaceutical and/or cosmetical compositions of the present invention can comprise 15 pharmaceutically and/or cosmetically acceptable additives. Suitable additives are diluents, dispersants and carriers of the active compounds. Additives other than water can include liquid and solid emollients, solvents, thickeners, emulsifiers, preservatives, coloring agents, opacifiers, sunscreens, and the like. The additives form the balance of the composition.

Emollients can be chosen from the group consisting of esters, fatty acids and alcohols, polyols, oils and waxes and are preferably present in amounts varying from 0.5 and 60 wt %.

Esters may be mono-, di- or triesters such as glyceryloleate, polyethylenglycolstearate, 20 dibutyladipate, diethylsebacate, dioctylsuccinate, triisopropyltrilinoleate or trilaurylcitrate. Esters may also be straight chain fatty acids such as laurylpalmitate, myristyllactate or stearyloleate; or branched chain fatty esters such as isopropylstearate or isostearylpalmitate.

Fatty acids and alcohols include those compounds having from 10 to 20 carbon atoms like for example cetyl-, myristyl-, palmitic- and stearyl-alcohols and -acids or lanolin alcohol.

25 Polyols may be linear or branched chain alkyl polyhydroxyl compounds like for example propylene glycol, sorbitol or glycerin or polymeric polyols such as polyethylenglycol (PEG).

Oils may be mineral oils like paraffin oil or vaseline, vegetable oils like almond oil, palm oil, avocado oil, castor oil or olive oil, silicone oils like for example dimethicone.

30 Waxes may be mineral waxes like paraffin wax, white wax, vaseline or ozokerite or animal waxes like woolfat or beeswax.

Solvents are preferably alcohols such as ethanol.

Thickeners will usually be present in amounts from 0.1 wt % to 20 wt %. Exemplary thickeners are gelatin or polyacrylamide.

Preservatives may include phenoxyethanol, paraben-compounds, chlorphenesin, EDTA, benzyllic alcohol, benzalkonium chloride and chlorhexidine.

5 Sunscreens include, in amounts varying from 0.1 wt % to 20 wt %, those materials commonly employed to block ultraviolet light, such as PARSOL® 1789 or PARSOL® MCX. Physical filters, such as micronized zinc oxide or titan dioxide, may also be included in the compositions of the present invention.

Emulsifiers may be incorporated into the compositions from about 0.1 wt % to 20 wt %.

10 Emulsifiers can be nonionic surfactants such as polyalkylene glycol ethers of fatty alcohols, anionic surfactants such as alkyl sulfates, fatty acid soaps, amphoteric surfactants such as dialkylamine oxide.

15 The composition according to the present invention is intended primarily as a product for topical application. The term "topical" as used in the present specification relates to the use of the above active compounds, which are processed with a suitable carrier material and which is applied to the skin, mucous membrane, hair and/or nails, so that it can display local activity. Accordingly, the topical forms embrace pharmaceutical and/or cosmetical dosage forms which are suitable for external use, so that a direct contact with the skin results. The topical dosage forms embrace gels, creams, lotions, salves, powders, aerosols, 20 emulsions, including oil in water and water in oil, and other conventional forms which are suitable for the direct application of products on the skin or mucous membrane. These dosage forms can be manufactured by mixing the above compounds with known carrier materials which are suitable for topical use.

25 Salves and creams contain oily, absorbent, water-soluble and/or emulsifying carrier materials such as vaseline, paraffin oil, propylene glycol, cetylalcohol, glycerine monostearate, alkyl-branched fatty acids and the like.

30 Lotions are liquid preparations and can vary from simple solutions to aqueous or aqueous/alcoholic preparations which contain the substances in finely divided form. The preparations contain suspended or dispersing substances such as, for example, sodium carboxymethylcellulose which suspend or disperse the active substance in a carrier prepared from water, alcohol, glycerine and the like.

Gels are semi-solid preparations which are obtained by gelling a solution or suspension of the active substance in a carrier material. The carrier materials, which can be hydrophilic

- 5 -

or hydrophobic, are gelled using a gelling agent in form of polymers of biological, natural or synthetical origin.

Aerosols are solutions or suspensions of the active substance in a carrier material which are applied using spray generators. Usually used carriers are, for example,

5 trichloromonofluoromethane, trichlorodifluoromethane, volatile silicones, nitrogen, etc..

Spays are solutions suspensions or powders of the active substance in a carrier material which are applied using mechanical pumps.

The compositions according to the present invention are used by applying an amount of the active compounds sufficient to provide a therapeutic and/or cosmetic effect to the skin

10 to be treated. This application can be effected in the usual manner by rubbing, spraying or by a plaster.

The topical compositions are usually applied in an amount to provide from 0.1 to 5 mg of active ingredient per  $\text{cm}^2$  of the skin per day.

The inventive combination can also be administered orally for stimulating collagen

15 synthesis in skin or for the treatment of chronic venous insufficiency and any other diseases originating from collagen deficiency. Oral administrations can be presented, for example, in the form of tablets, capsules, solutions, etc. For oral administration the compositions of the invention can be administered to adults in amounts of about 10-400 mg/day.

20 The present invention refers also to the use of a combination comprising from 0.5 to 1.5 wt % of one or more compounds selected from the group consisting of Titrated Extract of Centella Asiatica (TECA), asiaticoside, asiatic acid and madecassic acid, and from 4 to 6 wt % of pantothenic acid and/or its derivatives for the manufacture of medicaments and/or cosmetical compositions. Preferably, such medicaments and/or cosmetical compositions  
25 are used for treating wounds, chronic venous insufficiency, skin aging, wrinkling, laxity, cellulite and photodamage.

It is also an object of the present invention to provide a process for preparing the above pharmaceutical and/or cosmetical compositions, comprising mixing from 0.5 to 1.5 wt %

of one or more compounds selected from the group consisting of Titrated Extract of

30 Centella Asiatica (TECA), asiaticoside, asiatic acid and madecassic acid, and from 4 to 6 wt % of pantothenic acid and/or its derivatives.

The invention is illustrated in more detail by the following example.

- 6 -

Example: Bepanthen DECA

Dexpanthenol:	5.0g
Titrated Extract of Centella Asiatica (TECA):	1.0g
Paraffin Oil:	13.5g
5 Octyl stearate:	12.0g
Propylene glycol:	5.0g
Caprylic, capric, isostearic, adipic acids glycerol ester:	5.0g
Almond oil:	5.0g
PEG 30 dipolyhydroxystearate:	4.0g
10 PEG 22 dodecyl glycol copolymer:	3.0g
Glyceryl behenate:	3.0g
Microcrystalline wax:	2.0g
Paraffin wax:	1.5g
Cetostearyl alcohol:	1.0g
15 Pantolactone	0.5g
Magnesium sulfate:	0.5g
Phenoxyethanol:	0.3g
Chlorphenesin:	0.2g
Citric acid	0.004 g
20 Sodium chloride:	0.2g
Purified water:	up to 100 g

The above composition was applied to male and female human volunteers between 20 and 45 years on wounds created according to an artificial wound model (biopsies with a 3 mm punch). The wound healing degree was evaluated after 1, 3, 6 and 10 days of treatment, 25 with a scoring of epidermisation and dermis restructuring made on Dermascan® echographies. The evaluation of the wound status was carried out by means of video microscopic images taken at different times during the healing period.

Clinical results are shown in table 1, wherein the efficacy of Bepanthen Deca has been compared to that of Bepanthen Ointment (5% dexpanthenol) and Madecassol Cream (1% TECA). The results are expressed as wound healing degree, wherein 0.0 and 4.0 represent the lowest value (0% healing) and the highest value (100% healing), respectively.

Tab. 1 Clinical results

Composition	1 Day	3 Days	6 Days	10 Days
Bepanthen Deca	0.0	0.0	0.5	0.9

- 7 -

Bepanthen Ointment	0.0	0.1	0.4	0.6
Madecassol Cream	0.0	0.0	0.1	0.1

As shown in Table 1, a synergistic effect of dexpantenol and TECA is observed. After 10 days of treatment, the wound healing degree obtained using Bepanthen Deca is higher (0.9) than that which could be obtained by using the two compounds separately (0.6+0.1).

5 This unexpected synergy enables the use of low concentrations of active compounds, thereby reducing the patient's intolerance risks and the manufacturing costs of the medicament and/or cosmetical product.

Claims

1. Pharmaceutical and/or cosmetical composition comprising from 0.5 to 1.5 wt % of one or more compounds selected from the group consisting of Titrated Extract of Centella Asiatica (TECA), asiaticoside, asiatic acid and madecassic acid, and from 4 to 6 wt % of pantothenic acid and/or its derivatives.  
5
2. Pharmaceutical and/or cosmetical composition according to claim 1 comprising 0.5 to 1.5 wt % of TECA.
3. Pharmaceutical and/or cosmetical composition according to claim 2, comprising 1 wt % of TECA.  
10
4. Pharmaceutical and/or cosmetical composition according to any preceding claim, comprising from 4 to 6 wt % of dexpanthenol.
5. Pharmaceutical and/or cosmetical composition according to claim 4, comprising 5 wt % of dexpanthenol.  
15
6. Pharmaceutical composition according to any preceding claim, further comprising vitamins selected from the group consisting of vitamin A, vitamins B other than pantothenic acid, vitamin C and vitamin E.
7. Pharmaceutical composition according to any preceding claim, further comprising minerals for supporting the regeneration and maintenance of human tissues.  
20
8. Pharmaceutical and/or cosmetical composition according to any preceding claim, further comprising additives chosen from the group consisting of liquid and solid emollients, solvents, thickeners, emulsifiers, preservatives, coloring agents, opacifiers and sunscreens.
9. Pharmaceutical composition according to any preceding claim, further comprising active compounds for treating chronic venous insufficiency.  
25
10. Pharmaceutical composition according to claim 9, wherein the compound for treating chronic venous insufficiency is chosen from the group consisting of escin, rutosides and mixtures thereof.
11. Use of a combination comprising from 0.5 to 1.5 wt % of one or more compounds selected from the group consisting of Titrated Extract of Centella Asiatica (TECA), asiaticoside, asiatic acid and madecassic acid, and from 4 to 6 wt % of pantothenic acid  
30

- 9 -

and/or its derivatives for the manufacture of medicaments and/or cosmetical compositions.

12. Use according to claim 11 for treating wounds, chronic venous insufficiency, skin aging, wrinkling, laxity, cellulite and photodamage.
- 5 13. Process for preparing a pharmaceutical and/or cosmetical composition according to any one of claim 1 to 10, comprising mixing from 0.5 to 1.5 wt % of one or more compounds selected from the group consisting of Titrated Extract of Centella Asiatica (TECA), asiaticoside, asiatic acid and madecassic acid, and from 4 to 6 wt % of pantothenic acid and/or its derivatives.
- 10 14. The invention as hereinbefore described.

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/08742

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 A61K31/195 A61K35/78 A61K7/48 // (A61K35/78, 31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, BIOSIS, EMBASE, CHEM ABS Data, PHARMAPROJECTS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 852 946 A (PAOLI AMBROSI GIANFRANCO DE) 15 July 1998 (1998-07-15) *cf. abstract, page 3, lines 53 bridging with page 4, first line, and lines 14-18*	1-13
A	FR 2 770 776 A (LVMH RECH) 14 May 1999 (1999-05-14) *cf. page 5, lines 15-36 with page 6, lines 1-11*	1-13
A	FR 2 668 061 A (THOREL JEAN NOEL) 24 April 1992 (1992-04-24) *cf. abstract, page 4 and page 5, lines 1-18*	1-13

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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## INTERNATIONAL SEARCH REPORT

International Application No  
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 03676 A (CABO SOLER JOSE ; CALDERON GOMEZ JESUS (ES); PALACIOS GIL ANTUNANO) 6 February 1997 (1997-02-06) *cf. abstract, page 6, example 1, formulation 6* ---	1-13
A	US 5 945 109 A (SCHMIDT ALFRED ET AL) 31 August 1999 (1999-08-31) *cf. abstract, col. 1, last para., bridging with col. 2, first para.* ---	1-13

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/08742

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0852946 A	15-07-1998	IT	BS960094 A	29-05-1998
		CA	2219849 A	29-05-1998
		US	6147054 A	14-11-2000
FR 2770776 A	14-05-1999	EP	1028705 A	23-08-2000
		WO	9924009 A	20-05-1999
FR 2668061 A	24-04-1992	NONE		
WO 9703676 A	06-02-1997	ES	2098193 A	16-04-1997
		AU	6419696 A	18-02-1997
US 5945109 A	31-08-1999	AU	1793397 A	22-10-1997
		WO	9736570 A	09-10-1997
		EP	0907351 A	14-04-1999